REMARKS

Claims 18, 19, 22, 23, 26, and 26-44 are pending and stand rejected in the instant application. Claims 1-13 have been cancelled without prejudice as being drawn to a non-elected invention. Claims 26 and 34 have been cancelled without prejudice to the pursuance of same in a suitable continuing application. Claim 31 has been amended to correct a claim dependency. Applicant reserves the right to pursue the subject matter of the cancelled claims in this or another application. No new matter has been added by way of the amendments to the claims.

Applicant gratefully acknowledges the Examiner's withdrawal of certain outstanding rejections.

Claim Objections

Claim 36 was objected to as being a substantial duplicate of claim 31. Applicant has amended claim 31 to depend from claim 18. In view the amendment to claim 31, Applicant submits that claim 36 is no longer a substantial duplicate of claim 31 and respectfully requests reconsideration and withdrawal of the objection.

Rejection of Claims 26 and 34 Under 35 U.S.C. §112, Second Paragraph

Claims 26 and 34 have been rejected under 35 U.S.C. §112, second paragraph because, according to the Examiner, the phrase 'the substance normally operates an aberrant receptor' is unclear because "it is not clear how a synthetic substance 'normally operates' an aberrant receptor, since such a substance would not be a naturally occurring ligand."

Without conceding to the validity of the rejection, Applicant has cancelled claims 26 and 34, rendering the rejection of these claims under 35 U.S.C. §112, second paragraph moot. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of Claims 18, 19, 22, 23, 26, and 28-44 Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 18, 19, 22, 23, 26, and 28-44 under 35 U.S.C. §103(a) as being obvious over Lebrun et al., or Birnbaumer et al., or Green at al, or Kong et al, in view of Choong et al., and further in view of Dower et al., all previously of record. Applicant respectfully traverses this rejection for the reasons previously of record and for the reasons set forth below.

Claim 39, the first independent claim in the series, reads as follows, with emphasis added:

> Claim 39. A method of screening subject substances for **a substance capable of causing an aberrant receptor**, which has substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, **to operate in a manner similar to the non-aberrant receptor** comprising:
>
> 1) bringing the **aberrant receptor** into contact with **a subject substance**, said subject substance **comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,**
>
> 2) **determining the operation activity of said subject substance on said receptor,**
>
> 3) bringing the non-aberrant receptor into contact with a natural substance which operates the non-aberrant receptor and ,
>
> 4) determining the operation activity in (3), and
>
> 5) comparing the operation activity in step (2) with that of step (4), wherein a similar activity indicates that **the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor**.

No reasonable combination of any or all of the references of record discloses or suggests the claimed subject matter of the present claims.

The invention claimed in claim 39 is directed to a method of finding a synthetic substance which, when contacted with a aberrant receptor whose affinity for its natural substrate is impaired, causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. None of the references disclose or suggest that concept. The primary reference, Lebrun et al., doesn't even deal with mutant receptors having impaired binding for their natural substrate. The binding affinity of the Val^{382} insulin receptor was entirely normal. See, e.g., page 11276, right column, fourth paragraph.

Lebrun et al. designed extremely specific monoclonal antibodies which were directed to the C-terminus of the receptor. Lebrun et al. did not utilize synthetic substance, but used monoclonal antibodies. Lebrun et al. did not disclose or suggest that the monoclonal antibodies "failed to operate the nonaberrant receptor" as required by the claims. Thus Lebrun et al. did not compare the operation of such a substance on the aberrant receptor to the operation activity of the natural substance on the non-aberrant receptor, as required by all of the claims.

The other primary references are even less relevant than Lebrun et al. Birnbaumer et al., Green et al., Kong et al. and Choong et al. do not disclose or suggest finding a synthetic substance which can cause an aberrant receptor to operate similarly to a non-aberrant receptor by comparing the operating activity of (a) a substance which fails to operate the non-aberrant receptor, when placed in contact with the aberrant receptor, with (b) the non-aberrant receptor, in contact with its natural ligand. The Dower et al. patent does not remedy the defects of the other references, since it does not disclose or suggest the recited methods. Dower deals with recognition of binding ability, not comparison of the operating activity of (a) and (b) of the present claims.

All of the independent claims of Applicant's invention recite, as a required element, a method step comprising: bringing an aberrant receptor into contact with a subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor.

Additionally, independent claims 39, 40, and 44 require that the aberrant receptor have a substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, independent claims 42 and 43 require that the aberrant receptor have a substantially changed affinity for natural substances; and independent claim 41 requires that the aberrant receptor causes a disease by affecting the signal transduction system of a cell.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), every element of the claim under scrutiny must be disclosed or suggested in the cited references in such a manner that the proposed combination of teachings of the different references would have been suggested to one of ordinary skill in the art.

The Examiner also relies on Lebrun et al. as teaching "screening for compounds that would activate an insulin receptor that has a mutation that impairs the ability of the hormone to activate autophosphorylation of receptors and phosphorylation of substrates, the mutation not affecting the ligand binding extracellular portion of the receptor."

Applicant respectfully disagrees with the Examiner's interpretation of Lebrun et al. as teaching screening for compounds. Lebrun et al. does not in fact teach any 'screening assays', as this term is understood in the context of the pending claims. The goal of Lebrun et al. was to study a particular mutation (Val^{382}) and how it affected the function of the insulin receptor. Specifically, Lebrun et al. was attempting to study the role of conformational change in insulin receptor activation. The antibodies used by Lebrun et al. in their studies were purely *tools* to study this conformational change. Lebrun et al. was purely a *mechanistic* study, and not a search (i.e., a screening assay) for antibodies that could activate the mutant receptor.

Furthermore, the antibodies used by Lebrun et al. are not synthetic compounds, nor are they compounds which substantially fail to operate the non-aberrant receptor, as these antibodies were not tested on the non-aberrant receptor, and there is no reason to expect that they would not

operate the non-aberrant receptor if so tested. As discussed previously, the aberrant receptor studied in Lebrun et al. does not have a substantially changed affinity for insulin, the natural substance which normally operates the non-aberrant receptor.

The Examiner attempts to make up for these deficiencies by combining Lebrun et al. with Choong et al. and Dower et al. However, the Examiner also makes the assertion above that "[o]ne of skill in the art would have been motivated to use the screening assays of Lebrun et al. with an insulin receptor that affected ligand binding, even in the absence of a second reference that teaches a receptor with a mutation in the ligand binding domain". Applicant respectfully traverses this assertion, which appears to be hindsight reconstruction based on Applicant's disclosure. Applicant respectfully submits that it is the Examiner's responsibility to provide evidence that one of skill in the art would have been motivated to modify the methods of Lebrun et al., rather than simply stating so.

One of skill in the art would not be motivated to use the methods of Lebrun with an insulin receptor that affected ligand binding, because the methods of Lebrun are limited in usefulness to receptors having mutations affecting receptor **conformation**. One of the requirements for a rejection under 35 U.S.C. §103 is the reasonable expectation of success. Because the methods of Lebrun et al. would be scientifically unworkable using a receptor having a mutation affecting ligand binding, it is clear that there would be no reasonable expectation of success in trying to modify the methods of Lebrun et al. as the Examiner has proposed.

Moreover, contrary to the Examiner's assertion, one of skill in the art would certainly not have been motivated to use the "screening assays" of Lebrun et al., because Lebrun et al. does not in fact disclose any screening assays, but rather, discloses mechanistic studies, the methods of which are only useful for studying the function of the receptor.

On page 6 of the instant Office Action, the Examiner argues that it is irrelevant that Birnbaumer et al. "did not find a compound that caused the mutant type-2 vassopressin receptor to operate in a manner similar to the wild-type receptor", that "[i]t is the methods steps that are relevant, and that the result obtained in the prior art using those method stops is not relevant."

Applicant respectfully traverses the Examiner's position. The recitation in the pending claims, which appears in both the preamble and the final method step, that the compound "causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor" is an integral, required element of the claims. In describing this limitation as the "result" of the method steps of the pending claims, it appears that the Examiner views this limitation as merely an intended use. Applicant respectfully disagrees.

The instant claims are analogous to the method for growing and isoloating a particular swine virus at issue in Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation. 320 F.3d 1339 (C.A.Fed. (N.J.) 2003). In that case, the court held that "preamble language will limit the claim if it recites not merely a context in which the invention may be used but the essence of the invention without which performance of the recited steps is nothing but an academic exercise." Ibid. at 1345. The court further stated that

> This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself. Divorced from the process of growing and isolating virus, the claimed method reduces to nothing more than a process for producing cytopathic effects in sheets of cultured MA-104 cells-a process whose absence of fathomable utility rather suggests the academic exercise. Ibid. (emphasis in original)

The principle described by the court above applies to the instant claims. The identification of a compound which causes an aberrant receptor to operate in a manner similar to the non-aberrant receptor is the *raison d'être* of the pending claims.

Accordingly, as asserted by Applicant in previous responses, the disclosure of Birnbaumer et al. is not relevant to the pending claims because Birnbaumer et al. did not identify any compounds which cause the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

Furthermore, Birnbaumer et al. does not disclose the use of a synthetic compound which substantially fails to operate the non-aberrant receptor, as required by the claims. Kong et al. and Green et al. also do not disclose the use of a synthetic compound which substantially fails to operate the non-aberrant receptor, as required by the claims.

Applicant maintains the position that one of skill in the art would not have been motivated to combine the teachings of Choong et al. with any of Lebrun et al., Birnbaumer et al., Green at al, or Kong et al. Every one of these references is a mechanistic study of its respective receptor. In every case, the authors' use of compounds to investigate the activity of the receptors was in the furtherance of the goal of understanding the mechanistic action of the receptors. They were not screening for compounds that could operate the aberrant receptors in a manner similar to the non-aberrant receptors, as required by the instant claims. Furthermore, these references do not discuss the use or desirability of identifying drugs capable of causing the specific receptors disclosed therein to operate in a manner similar to the non-aberrant receptors, as required by the pending claims.

Even where a reference does discuss potential drug screening, it does not provide the motivation to combine references as the Examiner has suggested to arrive at Applicant's invention. For example, the last sentence of Kong et al. (page 23058, right column) discusses identification of antagonists to the unique antagonist binding discovered therein. However, the teaching is clearly that the receptor with a **normal** antagonist binding domain would be used in such screening, as opposed to a mutated

receptor. It is Applicant's position that this actually teaches away from Applicant's invention, which requires the use of an aberrant receptor.

Mechanistic studies of receptor action are highly specific to the types of receptors involved. In the cases of Lebrun et al., Birnbaumer et al., Green at al, and Kong et al., the respective receptors are transmembrane receptors, while Choong et al. is directed to the androgen receptor, which is a nuclear receptor. The mechanism of nuclear receptor action is fundamentally different from that of a transmembrane receptor. Accordingly, one of skill in the art reading the mechanistic studies of any of Lebrun et al., Birnbaumer et al., Green at al, or Kong et al. would have no motivation to combine the teachings of those references with those of Choong et al.

Applicant further traverses the Examiner's maintenance of the rejections over the references above further in view of Dower et al. The Examiner relies on Dower et al. to show the state of the art with respect to synthetic compounds and compound libraries, and to show that such compounds could be used in assays to identify therapeutic compounds, for example, those that bind receptors. According to the Examiner,

> one of skill in the art at the time of the invention would have been motivated to use the combinatorial chemistry screening methods of Dower et al., in which large numbers of synthetic (or natural) compounds could be rapidly and easily screened, in the receptor assays of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al., in view of Choong et al. in order to discover compounds that could activate a mutant receptor that could not be activated by a normal ligand, in order to find useful pharmaceuticals to treat diseases or disorders.

Applicant respectfully traverses the Examiner's position. As discussed above, Lebrun et al., Birnbaumer et al., Green at al, and Kong et al. simply are not screening assays as claimed in the instant invention. One skilled in this art would not have been motivated to combine these references with Dower because Dower is wholly unrelated to

the goals of theses references - namely, to investigate the mechanistic function of various receptors.

Additionally, the instant claims require the use of a synthetic compound which substantially fails to operate the non-aberrant receptor. Dower et al. provides no evidence that any synthetic compounds can operate or fail to operate any specific receptors. The requirement that the synthetic compound fail to operate the non-aberrant receptor is thus not present in any of the references cited by the Examiner. Without this required element of Applicant's claims, the cited references cannot support a rejection of the claims under 35 U.S.C. §103.

Based on the foregoing arguments, as well as the arguments set forth in prior responses, Applicant respectfully submits that the pending claims are not obvious over the cited art and respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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